

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BECKER, KURIG, STRAUS
Bavariastrasse 7
80336 Munich
ALLEMAGNE

Date of mailing (day/month/year) 21 September 2001 (21.09.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference NO 6555/WO	
International application No. PCT/EP00/04744	International filing date (day/month/year) 19 May 2000 (19.05.00)

1. The following indications appeared on record concerning:	
<input type="checkbox"/> the applicant	<input type="checkbox"/> the inventor
<input checked="" type="checkbox"/> the agent	<input type="checkbox"/> the common representative
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The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Jean-Marie MCADAMS Telephone No.: (41-22) 338.83.38
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- (71) Applicant (*for all designated States except US*): SOCIETE DES PRODUITS NESTLE S.A. [CH/CH]; P.O. Box 353, CH-1800 Vevey (CH).
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(54) Title: METHOD FOR INCREASING PROPIONATE IN THE GASTRO-INTESTINAL TRACT

(57) Abstract: A method for selectively increasing the production of propionate in the gastro-intestinal tract of a mammal. The method includes the step of enterally administering to the mammal a nutritional composition which contains dextran. Increasing the propionate production results in decreased blood cholesterol levels, decreased blood triglyceride levels, decreased very low density lipoprotein levels, increased high density lipoprotein levels, and increased insulin sensitivity.

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**Method for Increasing Propionate
in the Gastro-Intestinal Tract**

Summary of the invention

Accordingly, in one aspect, this invention provides a method for selectively increasing the production of propionate in the gastro-intestinal tract, the method comprising enterally administering to a mammal a nutritional composition which contains dextran.

It has been surprisingly found that dextran, when fermented by micro-organisms which occur in the gastro-intestinal tract, results in the increased production of propionate when compared to other non-digestible polysaccharides. Therefore, dextran is an ideal source of propionate in the gastro-intestinal tract.

The term "dextran" means a group of polysaccharide which are composed of α -D-glucopyranosyl units linked predominantly α -D(1 \rightarrow 6). Dextrans are produced by certain types bacteria growing on a glucose substrate; for example *Leuconostoc mesenteroides*, *Leuconostoc dextranicum*, and *Leuconostoc mesenteroides ssp. cremoris*. Further, shorter chain dextrans may be obtained by hydrolysing native dextrans or by synthesising them.

In another aspect, this invention provides a method for decreasing blood cholesterol levels in a mammal, the method comprising enterally administering to a mammal a nutritional composition which contains dextran.

In another aspect, this invention provides a method for decreasing blood triglyceride levels in a mammal, the method comprising enterally administering to a mammal a nutritional composition which contains dextran.

In another aspect, this invention provides a method for decreasing very low density lipoprotein levels in a mammal, the method comprising enterally administering to a mammal a nutritional composition which contains dextran.

In another aspect, this invention provides a method for increasing high density lipoprotein levels in a mammal, the method comprising enterally administering to a mammal a nutritional composition which contains dextran.

In another aspect, this invention provides a method for increasing insulin sensitivity in a mammal, the method comprising enterally administering to a mammal a nutritional composition which contains dextran.

Detailed Description of the Preferred Embodiments

Embodiments of the invention are now described, by way of example only.

This invention is based upon the discovery that the colonic fermentation of dextran by micro-organisms results in the production of relatively larger amounts of propionate as compared to other non-digestible polysaccharides. Therefore, the enteral administration of dextran provides a convenient and simple way of selectively increasing the production of propionate in the gastro-intestinal tract.

The dextran used may be any suitable dextran; natural, synthetic or partially hydrolysed. Suitable dextrans are commercially available or may be produced by growing *Leuconostoc* micro-organisms on a sucrose substrate and isolating and purifying the dextran. Alternatively, the dextran may be produced as described in European patent application 0881283.

Preferably, however, the dextran is a high molecular weight dextran; for example having a molecular weight above 50000, preferably above about 70000, more preferably above about 100000; for example above about 500000.

The dextran may be formulated into any suitable nutritional composition as desired since the exact composition and form is not critical. One suitable class of nutritional compositions is food products. Examples of suitable food products include yoghurts, ice cream confections, milk-based drinks, salad dressings, sauces, toppings, desserts, confectionery products, biscuits, cereal-based snack bars, prepared dishes, and the like. For humans, food products which are convenience foods are preferred since patient compliance is increased. Another suitable class of nutritional compositions is nutritional formulas such as enteral formulas for clinical and infant nutrition, and nutritional supplements. For pets, the nutritional compositions may be in the form of pet foods such as dried kibbles and retorted wet products.

The nutritional compositions may contain other ingredients as desired. For example, the nutritional compositions may contain other polysaccharides such as insoluble and soluble fibres. Fibres are known to have a beneficial effect upon cholesterol and glucose levels. Suitable sources of soluble and insoluble fibres are commercially available.

An example of a suitable fibre is inulin or its hydrolysis products. The inulin may be provided in the form of a natural extract which is suitable for human consumption. Suitable inulin extracts may be obtained from Orafit SA of Tirlemont 3300, Belgium under the trade mark "Raftiline". For example, the inulin may be provided in the form of Raftiline®ST which is a fine white powder which contains about 90 to about 94% by weight of inulin, up to about 4% by weight of glucose and fructose, and about 4 to 9% by weight of sucrose. The

averag degree of polymerisation of the inulin is about 10 to about 12. The hydrolysis products of inulin are fructo-oligosaccharides in the form of fructos oligomers containing 1-kestose(GF2), nystose(GF3), and 1F-fructofuranosyl nystose(GF4), in which fructosyl units(F) are bound at the β -2,1 position of sucrose(GF) respectively. The fructo-oligosaccharides may be obtained commercially, for example from Orafit SA of Tirlemont 3300, Belgium under the trade mark "Raftilose", or from Meiji Seika Co. of Japan. For example, the fructo-oligosaccharides may be provided in the form of Raftilose®P95. Other oligosaccharides may be included if desired. Suitable examples are galacto-oligosaccharides, xylo-oligosaccharides or oligo derivatives of starch.

If both soluble and insoluble fibre are used, the ratio of soluble fibre to insoluble fibre is preferably about 1:3 to about 3:1; more preferably about 1:1 to about 2:1.

The nutritional composition may also contain vitamins and minerals as desired. For clinical applications, the nutritional composition preferably includes a complete vitamin and mineral profile. For example, sufficient vitamins and minerals may be provided to supply about 25% to about 250% of the recommended daily allowance of the vitamins and minerals per 1000 calories of the nutritional composition.

When the nutritional composition is in the form of a food product or nutritional formula, the nutritional composition may contain a protein source, a lipid source and a carbohydrate source. These sources may be selected as desired.

The lipid source is preferably rich in monounsaturated fatty acids; for example monounsaturated fatty acids may provide at least 50% of energy of the lipid source. The lipid source may also contain polyunsaturated fatty acids (omega-3 and omega-6 fatty acids). The lipid profile is preferably designed to have a polyunsaturated fatty acid omega-6 (n-6) to omega-3 (n-3) ratio of about 4:1 to about 10:1. Saturated fatty acids preferably provide less than 20% of the energy of the lipid source; for example less than about 15%.

The nutritional composition may be used in the nutritional management of conditions such as diabetes and hypercholesterolemia.

The amount of the nutritional composition required to be fed to a patient will vary depending upon factors such as the patient's condition, the patient's body weight, the age of the patient, and whether the nutritional composition is the sole source of nutrition. However the required amount may be readily set by

a medical practitioner. In general, sufficient of the nutritional composition is administered to provide the patient with up to about 40 g of dietary fibre (insoluble and soluble) per day; for example about 25 g to about 35 g of dietary fibre per day. The amount of dextran that the patient receives is preferably in the
5 range of about 2g to about 15g per day. If the nutritional formula is used as a supplement to other foods, the amount of the nutritional composition that is administered daily may be decreased accordingly.

The nutritional composition may be taken in multiple doses, for example 2 to 5 times, to make up the required daily amount or may taken in a single dose.
10 The nutritional composition may also be fed continuously over a desired period.

The invention is now further described with reference to the following specific examples.

15 Example 1

Three non-digestible polysaccharides are fermented in an *in vitro* fermentation model which simulates fermentation conditions in the gastro-intestinal tract. The polysaccharides are (i) acacia gum (available under the trade
20 name Fibregum), (ii) Dextran produced according to European patent application 0881283, and (iii) lactulose.

For each polysaccharide, an amount of 100 mg of the polysaccharide is added to 8 ml of a carbonate-phosphate buffer, which contains oligo-elements, in a 50 ml air-tight flask. The composition of the buffer is as follows:-

C mponent	Am unt
NaHCO ₃	9.240g/l
Na ₂ HPO ₄ · 12H ₂ O	7.125g/l
NaCl	0.470g/l
KCl	0.450g/l
Urea	0.400g/l
CaCl ₂ · 6H ₂ O	0.108g/l
Na ₂ SO ₄	0.100g/l
MgCl ₂ · 6H ₂ O	0.100g/l
FeSO ₄ · 7H ₂ O	36.80mg/l
MnSO ₄ · H ₂ O	11.59mg/l
ZnSO ₄ · 7H ₂ O	4.40mg/l
CoCl ₂ · 6H ₂ O	1.20mg/l
NiCl ₂	1.00mg/l
CuSO ₄ · 5H ₂ O	0.98mg/l
Mo ₇ (NH ₄) ₆ O ₂₄ · 4H ₂ O	0.17mg/l
Resazurine	1.00mg/l

Each flask is rinsed for 1 minute with CO₂ gas and stored at 4°C for 16 hours under a slight over-pressure.

- 5 Dilute human faeces is prepared from samples of fresh faeces collected from healthy humans not having consumed antibiotics for at least 3 months and not producing methane. The faeces are immediately rinsed with CO₂ gas, and 3 parts (weight/weight) of the carbonate-phosphate buffer with oligo-elements are rapidly added at 37°C. The mixture is blended for 2 minutes in a stomacher
- 10 (Stomacher 400, Seward, London, GB) and filtered by a Polymon PES1000/45 filter with 1 mm holes (Schweizerische Seidenfabrik SA, Zürich, CH).

- An amount of 2 ml of the dilute faeces is added to each flask and the head space gas is replaced by a flux of temperate CO₂ gas for 1 minute. After equilibration of the pressure, each flask is sealed air-tight and incubated in an
- 15 agitated water bath at 37°C.

After 24 hours, the content of short chain fatty acids in the flasks determined twice by direct injection of an acidified and sterile filtered sample on a gas chromatograph with FID (HP 8960, Hewlett Packard, Urdorf, CH) fitted

with a DB-FFAP capillary column (MSP FRIEDLI & Co, Koeniz, CH). The results are as follows:-

Polysaccharide	Short Chain fatty acid	SCFA Content ($\mu\text{mol}/100\text{mg}$)	SCFA % of total*
Fibregum	Acetate	648.2	63.7
	Propionate	228.6	22.5
	Butyrate	107.1	10.5
Dextran	Acetate	415.0	46.3
	Propionate	363.5	40.6
	Butyrate	87.6	9.8
Lactulose	Acetate	909.2	74.6
	Propionate	111.7	9.2
	Butyrate	172.2	14.1

- 5 * the percentages do not added up to 100% since other short chain fatty acids are present in minor amounts.

10 The results indicate that fermentation of dextran results in increased production of propionate; relatively and absolutely. For the other polysaccharides, only acetate was favoured.

Example 2

15 A study is undertaken with 45 mice aged between 7 and 10 weeks. The mice are kept in sterile conditions in cages. The mice have free access to water and a standard diet.

20 On the first day of the study, each mouse is fed 0.5 ml of a complete human microbial flora, diluted 100 times, by intra-gastric tube. The feeding is repeated on day 2. On day 11, the mice are separated into three groups; each group being housed in a separate sterile isolation unit.

On day 15, each group of mice receives a test diet. The test diets are sterile. The test diets all contain a potato puree, sugar, fish meal, cellulose, vitamins and minerals and a non-digestible polysaccharide. The polysaccharides are as follows:-

Diet	P lysaccharide
Positive Control	Fructo-oligosaccharide (Raftilose)
Negative Control	Cellulose
Diet 1	Dextran

The mice are fed the diets until day 36. During this time, the development of the intestinal flora of each mouse is monitored by collecting faeces and determining microbial counts. A blood sample is collected from each mouse and analysed for short chain fatty acids. The mice are then anaesthetised and sacrificed. The caecum and stomach contents of each mouse is removed and analysed for short chain fatty acids and microbial flora, respectively.

All mice fed Diet 1 have relatively higher levels of propionate in the blood and caecum.

Example 3

A study was performed to evaluate with 3 to 5 volunteers whether a significant increase of propionic acid could be measured in feces after consumption of an acute dose of 15g Dextran T2000 and a chronic dose of 10g Dextran T2000 per day.

This study was performed as a randomized placebo-controlled double blind study with 4 volunteers in a cross-over design. SCFAs were measured in feces. Additionally, blood formula and selected blood proteins were measured before and after consumption of the dextran.

Outline of Results

- a) the effect of an acute dose of 15g dextran on propionic acid in feces was investigated. The pool of feces collected between 12 and 72 hours after consumption of the acute dose was analysed for short chain fatty acids (SCFAs). Taking the average results of the 4 volunteers, propionic acid in feces of the pool increased by 3.43 mmol in the treatment group relative to the placebo group.
- b) a chronic consumption of 10g dextran per day was investigated. Propionic acid concentration in a fecal sample was analysed after 1 week of chronic consumption. Taking the average of the 4 volunteers, propionic acid concentration increased by 24.0 $\mu\text{mol/g}$ dry feces in the treatment group compared to a decrease of 5.7 $\mu\text{mol/g}$ dry feces in the placebo group.

Consumption of dextran induced no relevant changes of blood formula, investigated blood proteins or blood plasma enzymes. No clinical symptoms have been reported.

Conclusions

- 5 The results indicate an increase in the level of propionic acid in the gastrointestinal tract following consumption of dextran.

Results

- 10 A summary of results from the study on dextran is set out below. This was a placebo controlled double blind study with a cross-over design. 4 volunteers were enrolled.

- 15 Results are given separately for treatment (Dextran) and placebo (maltodextrin). Additionally results relative to placebo are given.

fecal samples (1 week intake of 10g per day)

fecal samples (1 week intake of 10g per day)					C2: acetic acid	C3: propionic acid
Treatment					In average:	
volunteer	plonate conc.	C3/C2	% propionic acid			
1	89.89	-0.139	0.1			
2	-13.73	-0.087	-2.7			
3	1.31	0.071	6.8			
4	18.43	0.007	3.3			
av	23.98 $\mu\text{mol/g dry}$	-0.037	1.9			
Placebo						
volunteer	plonate conc.	C3/C2	% propionic acid			
1	11.39	-0.027	-0.7			
2	-2.35	-0.144	-4.6			
3	-27.51	-0.041	-0.9			
4	-4.36	-0.002	-0.2			
av	-5.71 $\mu\text{mol/g dry}$	-0.054	-1.6			
treatm - plac.						
volunteer		C3/C2	% propionic acid			
1	78.50	-0.112	0.8			
2	-11.38	0.057	1.9			
3	28.82	0.112	7.7			
4	22.79	0.009	3.5			
av	29.68 $\mu\text{mol/g dr}$	0.02	3.5			
Relative to placebo, propionate concentration increased by 29.7 $\mu\text{mol/gdry feces}$.						
Relative to placebo, propionate/acetate ration increased by 0.02.						
Relative to placebo, %age of propionate on total SCFAs increased by 3.5%.						

po I f feces (12h to 72h after intake of 15g)					In blood, no changes in SCFA concentrations were observed.	
treatment					In average:	
	C3 produce	C3 in tot	C3/C2	conc. C3 (µmol/g wet)		
1	29.65	30.32	0.57	35.54		
2	2.26	20.98	0.39	8.61	During treatment, propionate production was 10.8 mmol.	
3	8.41	22.31	0.47	35.86	During treatment, %age of propionate on total SCFAs was 23%.	
4	2.91	18.20	0.34	13.88	During treatment, propionate by acetate ratio 0.44.	
av	10.81	22.95	0.44	23.47	During treatment, propionate concentration was 23.5 µmol/g wet feces.	
placebo						
	C3 produce	C3 in tot	C3/C2	conc. C3 (µmol/g wet)		
1	17.11	24.84	0.44	26.84		
2	3.91	18.13	0.35	11.97	During treatment, propionate production was 7.4 mmol.	
3	4.46	22.37	0.48	22.96	During treatment, %age of propionate on total SCFAs was 20.4%.	
4	4.04	16.39	0.27	10.35	During treatment, propionate by acetate ratio 0.39.	
av	7.38	20.43	0.39	18.03	During treatment, propionate concentration was 18.0 µmol/g wet feces.	
treatment - placebo						
	C3 produce	C3 in tot	C3/C2	conc. C3 (µmol/g wet)		
1	12.54	5.48	0.13	8.69		
2	-1.65	2.84	0.04	-3.37	Relative to placebo, propionate production increased by 3.4 mmol.	
3	3.95	-0.06	-0.01	12.90	Relative to placebo, %age of propionate on total SCFAs increased by 2.5%.	
4	-1.12	1.81	0.06	3.53	Relative to placebo, propionate/acetate ratio increased by 0.06 (or 15%).	
av	3.43	2.52	0.06 (=+15%)	5.44	Relative to placebo, propionate concentration increased by 5.4 µmol/g wet feces.	

Claims

- 5 1. The use of dextran in the preparation of a nutritional composition for selectively increasing the production of propionate in the gastro-intestinal tract of a mammal.
- 10 2. The use of dextran in the preparation of a nutritional composition for decreasing blood cholesterol levels in a mammal.
- 10 3. The use of dextran in the preparation of a nutritional composition for decreasing blood triglyceride levels in a mammal.
- 15 4. The use of dextran in the preparation of a nutritional composition for decreasing very low density lipoprotein levels in a mammal.
- 15 5. The use of dextran in the preparation of a nutritional composition for increasing high density lipoprotein levels in a mammal.
- 20 6. The use of dextran in the preparation of a nutritional composition for increasing insulin sensitivity in a mammal.
- 25 7. The use according to any of claims 1 to 6 in which the dextran is a high molecular weight dextran having a molecular weight above about 500000.
- 25 8. The use according to any of claims 1 to 7 in which the nutritional composition further comprises inulin, fructo-oligo saccharide, galacto-oligosaccharides, or xylo-oligosaccharides, or mixtures thereof.
- 30 9. The use according to any of claims 1 to 8 in which the nutritional composition further comprises a lipid source which is rich in monounsaturated fatty acids and poor in saturated fatty acids.

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/EP 00/04744

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A23L1/054 A23L1/308 A23L1/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, FSTA, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 382 355 A (HAYASHIBARA) 16 August 1990 (1990-08-16) page 1, line 10-25 page 2, line 32-35 page 9, line 10-13 page 9, line 16-19	1-9
Y	claims 1,2,6,7,9,12,13	1-5
X	EP 0 153 013 A (FISONS) 28 August 1985 (1985-08-28) page 2, line 15-19 page 3, line 20 -page 4, line 12 page 4, line 10-17 page 5, line 7-10 page 6, line 23-25 page 7, line 18,19 claims 1-9	1-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

In .ational Application No

PCT/EP 00/04744

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 010, no. 043 (C-329), 20 February 1986 (1986-02-20) & JP 60 190717 A (MEITOU SANGYO KK), 28 September 1985 (1985-09-28) abstract	1-5
A	D.SOUTHGATE ET AL.: "Dietary Fibre:Chemical and biological Aspects" 1990 , ROYAL SOCIETY OF CHEMISTR , CAMBRIDGE,GB XP002122986 pages 340-343 page 340, paragraph 3 page 341, paragraph 2 page 343, line 16-26	1-9
A	D.MC CORMICK ET AL: "Annual Review of Nutrition" , ANNUAL REVIEWS , PALO ALTO,CALIFORNIA,USA XP002123057 cited in the application pages 117-143 page 123, paragraph 2 page 126, paragraph 1 page 129, paragraph 3 -page 130, paragraph 1 page 131, paragraph 3 - paragraph 4	1-8
A	EP 0 881 283 A (NESTLE) 2 December 1998 (1998-12-02) cited in the application claims	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/04744

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 382355 A	16-08-1990	JP 2289520 A	29-11-1990
		JP 2779963 B	23-07-1998
		CA 2007270 A	09-08-1990
		DE 69031285 D	25-09-1997
		DE 69031285 T	12-02-1998
EP 153013 A	28-08-1985	AT 56148 T	15-09-1990
		AU 571641 B	21-04-1988
		AU 3819385 A	08-08-1985
		DE 3579471 D	11-10-1990
		DK 39685 A	02-08-1985
		JP 60188403 A	25-09-1985
JP 60190717 A	28-09-1985	JP 1797796 C	28-10-1993
		JP 5002652 B	13-01-1993
EP 881283 A	02-12-1998	AU 6901598 A	03-12-1998
		BR 9801736 A	11-01-2000
		CA 2233411 A	30-11-1998
		CN 1201039 A	09-12-1998
		CZ 9801669 A	13-01-1999
		HU 9801263 A	28-07-1999
		JP 11009266 A	19-01-1999
		NO 982004 A	01-12-1998
		NZ 330239 A	28-01-1999
		PL 326483 A	07-12-1998
		US 6004800 A	21-12-1999

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference NO 6555/WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/04744	International filing date (day/month/year) 19/05/2000	Priority date (day/month/year) 20/05/1999
International Patent Classification (IPC) or national classification and IPC A23L1/054		
Applicant SOCIETE DES PRODUITS NESTLE S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 13/12/2000	Date of completion of this report 13.09.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Graham, J Telephone No. +49 89 2399 7368 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/04744

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-11 as originally filed

Claims, No.:

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/04744

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 4 - 6, 8
	No:	Claims	2, 3, 7, 9
Inventive step (IS)	Yes:	Claims	1, 4 - 6
	No:	Claims	2, 3, 7 - 9
Industrial applicability (IA)	Yes:	Claims	1 - 9
	No:	Claims	

2. Citations and explanations: **see separate sheet**

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/04744

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are referred to:

D1: EP-A-0 382 355 (HAYASHIBARA) 16 August 1990 (1990-08-16)

D2: PATENT ABSTRACTS OF JAPAN vol. 010, no. 043 (C-329), 20 February 1986 (1986-02-20) & JP 60 190717 A (MEITOU SANGYO KK), 28 September 1985 (1985-09-28)

D2': JP 60 190717 A (MEITOU SANGYO KK), 28 September 1985 (1985-09-28), translation into English provided by the Applicant

D3: D.SOUTHGATE ET AL.: 'Dietary Fibre:Chemical and biological Aspects' 1990 , ROYAL SOCIETY OF CHEMISTR , CAMBRIDGE,GB XP002122986

1.0 Novelty (Article 33(2) PCT)

1.1 The subject matter of claim 1 is rendered novel since none of the prior art documents D1 to D3 disclose the use of dextran in the preparation of a nutritional composition for selectively increasing the production of propionate in the gastro-intestinal tract of a mammal.

1.2 The subject matter of claims 2 and 3 defines the use of dextran in the preparation of a nutritional composition for decreasing blood cholesterol and blood triglyceride levels in a mammal respectively. D2' (p. 5, 5 & 6th para., p. 7, 2nd para.) which discloses the use of partially degraded dextran with an intrinsic viscosity of 0.29 - 1.1, corresponding to the molecular weight range of 100,000 - 1,500,000, having a marked effect in lowering blood triglyceride and cholesterol renders the subject matter of claims 2 and 3 not novel. It follows that the subject matter of claim 7 is also not novel.

1.3 The subject matter of claims 4 and 5 is rendered novel since neither D1 to D3 disclose the use of dextran for decreasing very low density lipoprotein levels and increasing high density lipoprotein levels in a mammal respectively.

1.4 The subject matter of claim 6 is rendered novel since none of the prior art D1 to D3

disclose the use of dextran in the preparation of a nutritional composition for increasing insulin sensitivity in a mammal.

1.5 The wording of the present claim 9 is such that a composition comprising dextran and monounsaturated fatty acids used according to any of claims 1 to 8 is novelty destroying. D2' renders the subject matter of claim 9 not novel, since it uses compositions (experimental e.x. 1 - 3) comprising dextran and corn oil, which is an oleic acid source, to suppress an increase in serum triglyceride and cholesterol.

2.0 Inventive Step (Article 33(3) PCT)

2.1 The subject matter of claim 1 is deemed to involve an inventive step since none of the prior art teaches the use of dextran specifically for selectively increasing the production of propionate in the gastro-intestinal tract of a mammal.

2.2 The subject matter of claims 4 and 5 are deemed to involve an inventive step since none of the prior art teaches the use of dextran for decreasing very low density lipoproteins and increasing high density lipoprotein in mammals respectively.

2.3 The subject matter of claim 6 is considered as to involving an inventive step. D3 which is considered as the closest prior art teaches the use of viscous polysaccharides to increase insulin sensitivity in mammals but not dextran specifically. However, the comparative examples in the application as originally filed show dextran amongst other non-digestible polysaccharides to produce more propionic acid, thus, demonstrating an unexpected technical effect.

2.4 The subject matter of claim 8 relates to the use according to any of claims 1 to 7 wherein the composition comprises a further oligosaccharide. D2' which is considered as the closest prior art, teaches the use of use of partially degraded dextran having a marked effect in lowering blood triglyceride and cholesterol.

The technical problem to be solved by the present application concerns the increase in propionic acid in the gastro-intestinal tract of mammals.

Since the additional oligosaccharides do not contribute to solving the technical problem and do not provide an unexpected technical effect, the subject matter of claim 8 cannot

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/04744

be considered as to involving an inventive step.

3.0 Industrial Applicability (Article 33(4) PCT)

For the assessment of the present claims 1 to 9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference NO 6555/WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 00/04744	International filing date (day/month/year) 19/05/2000	(Earliest) Priority Date (day/month/year) 20/05/1999
Applicant SOCIETE DES PRODUITS NESTLE S.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the applicant specific instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A23L1/054 A23L1/308 A23L1/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, FSTA, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 382 355 A (HAYASHIBARA) 16 August 1990 (1990-08-16) page 1, line 10-25 page 2, line 32-35 page 9, line 10-13 page 9, line 16-19 claims 1,2,6,7,9,12,13	1-9
Y	---	1-5
X	EP 0 153 013 A (FISONS) 28 August 1985 (1985-08-28) page 2, line 15-19 page 3, line 20 -page 4, line 12 page 4, line 10-17 page 5, line 7-10 page 6, line 23-25 page 7, line 18,19 claims 1-9	1-8

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

18 October 2000

Date of mailing of the international search report

25/10/2000

Name and mailing address of the ISA

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Authorized officer

Tallgren, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 010, no. 043 (C-329), 20 February 1986 (1986-02-20) & JP 60 190717 A (MEITOU SANGYO KK), 28 September 1985 (1985-09-28) abstract	1-5
A	D.SOUTHGATE ET AL.: "Dietary Fibre:Chemical and biological Aspects" 1990 , ROYAL SOCIETY OF CHEMISTR , CAMBRIDGE,GB XP002122986 pages 340-343 page 340, paragraph 3 page 341, paragraph 2 page 343, line 16-26	1-9
A	D.MC CORMICK ET AL: "Annual Review of Nutrition" , ANNUAL REVIEWS , PALO ALTO,CALIFORNIA,USA XP002123057 cited in the application pages 117-143 page 123, paragraph 2 page 126, paragraph 1 page 129, paragraph 3 -page 130, paragraph 1 page 131, paragraph 3 - paragraph 4	1-8
A	EP 0 881 283 A (NESTLE) 2 December 1998 (1998-12-02) cited in the application claims	1-9

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 382355	A	16-08-1990	JP 2289520	A	29-11-1990
			JP 2779963	B	23-07-1998
			CA 2007270	A	09-08-1990
			DE 69031285	D	25-09-1997
			DE 69031285	T	12-02-1998
EP 153013	A	28-08-1985	AT 56148	T	15-09-1990
			AU 571641	B	21-04-1988
			AU 3819385	A	08-08-1985
			DE 3579471	D	11-10-1990
			DK 39685	A	02-08-1985
			JP 60188403	A	25-09-1985
JP 60190717	A	28-09-1985	JP 1797796	C	28-10-1993
			JP 5002652	B	13-01-1993
EP 881283	A	02-12-1998	AU 6901598	A	03-12-1998
			BR 9801736	A	11-01-2000
			CA 2233411	A	30-11-1998
			CN 1201039	A	09-12-1998
			CZ 9801669	A	13-01-1999
			HU 9801263	A	28-07-1999
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			NO 982004	A	01-12-1998
			NZ 330239	A	28-01-1999
			PL 326483	A	07-12-1998
			US 6004800	A	21-12-1999